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Study of Antimicrobial Quinolones and Structure Activity Relationship of Anti-Tubercular Compounds

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Review Article

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ABSTRACT

Fluoroquinolones (FQs) are an important synthetic antimicrobial agents being clinically used. Currently some FQs are under investigation for the treatment of multidrug-resistant tuberculosis (MDR-TB) and extensive drug resistance (XDR-TB) and are under investigation as first-line drugs. Their main biological target in *Mycobacterium tuberculosis* is the DNA gyrase, a topoisomerase II encoded by *gyrA* and *gyrB* that is essential to maintain the DNA supercoil. The mutations in short regions of DNA gyrase are associated with quinolone resistance or hyper susceptibility and take place in several MDR clinical isolates of *M. tuberculosis*. The anti-TB property mode of action and structure activity relationship studies of the some known quinolone derivatives are studied. Furthermore, the activity of quinolones as new class of potent and selective anti-TB agents, particularly their activity against MDR-TB and XDR-TB.

INTRODUCTION

The first quinolone, nalidixic acid, was isolated as a by-product of the synthesis of chloroquine and used for the treatment of urinary tract infections (UTIs) for many years. The fluorinated-quinolones, like ciprofloxacin (CPFX), moxifloxacin (MFLX), and gatifloxacin (GFLX) have broad spectrum antimicrobial activity for the treatment of various pathogenic diseases. Relatively few side effects appear comes with the use of these fluoroquinolones (FQs). Microbial resistance may be developed. Rare and potentially fatal side effects have also resulted. Due to side effects the withdrawal from the market of temafloxacin (immune hemolytic anemia), trovafloxacin (hepatotoxicity), grepafloxacin (cardiotoxicity), and clinafloxacin (phototoxicity) [1].

Tuberculosis (TB) is one of the most common infectious diseases, with about one-third of world's population infected with Mycobacterium tuberculosis (Global Tuberculosis Control, 2011). Even more frightening is the emergence of extensively drug resistant TB (XDR-TB) reported in all regions of the world. The increased number of MDR strains, is closely associated to the growing global HIV/AIDS pandemic [2,3]. The association of TB and HIV infections is so dramatic that, nearly two-thirds of the patients diagnosed with TB are also HIV-1 positive [4] and the risk of developing TB is between 20 and 37 times greater in people living with HIV than among those who do not have HIV infection [5,6]. TB is the leading cause of death among HIV infected people; the WHO estimates that TB accounts for more than a quarter of deaths among people living with HIV worldwide [7]. Since HIV infection is a major risk factor for the development of active TB which, in turn is a cofactor in the progression of HIV infection [8].

ANTIBACTERIAL SPECTRUM

The FQs are potent bactericidal agents against *E. coli* and various species of *Salmonella, Shigella, Enterobacter, Campylobacter,* and *Neisseria*. Ciprofloxacin (CPFX) is more active than norfloxacin against *P. aeruginosa.* The FQs also have good activity against staphylococci, but not against methicillin-resistant strains. Activity against streptococci is limited to a subset of the quinolones, including levofloxacin (LVFX), GFLX, and MFLX [9]. Several intracellular bacteria are inhibited by FQs; these include species of *Chlamydia, Mycoplasma, Legionella, Brucella,* and *Mycobacterium* [10]. Ciprofloxacin (CPFX), ofloxacin (OFLX),

and pefloxacin have MIC_{90} values from 0.5 to 3 mg/ml for *M. fortuitum, M. kansasii,* and *M. tuberculosis;* OFLX and pefloxacin are active in leprosy [11]. Several of FQs have activity against anaerobic bacteria, like garenoxacin and gemifloxacin [12]. Resistance to quinolones may develop during therapy *via* mutations in the bacterial chromosomal genes encoding DNA gyrase or topoisomerase IV or by active transport of the drug out of the bacteria [13]. Resistance has increased after the introduction of FQs, especially in *Pseudomonas* and staphylococci [14]. Increasing FQ resistance also is being observed in *C. jejuni, Salmonella, N. gonorrhoeae,* and *S. pneumonia* [15]. The FQs are concentration-dependent agents, resulting in bacterial eradication when unbound serum area-under-the-curve-to-MIC ratios exceed 25 to 30.

MECHANISM OF ACTION QUINOLONES

The quinolone antibiotics target bacterial DNA gyrase and topoisomerase IV [16]. For many gram-positive bacteria (such as *S. aureus*), topoisomerase IV is the primary activity inhibited by the FQs. In contrast, for many gram-negative bacteria (such as *E. coli*), DNA gyrase is the primary quinolone target [17]. To combat this problem, the bacterial enzyme DNA gyrase is responsible for the permanent introduction of negative supercoils into DNA. This is an ATP-dependent reaction requiring that both strands of the DNA be cut to permit passage of a segment of DNA through the break; the break then is resealed. The drugs inhibit gyrase-mediated DNA supercoiling at concentrations that correlate well with those required to inhibit bacterial growth. Mutations of the gene that encodes the A subunit polypeptide can confer resistance to these drugs [11,16]. This enzyme is the target for some antineoplastic agents. Quinolones inhibit eukaryotic type II topoisomerase only at much higher concentrations (100 to 1000 mg/ml) [18].

Bacterial resistance

Gram-positive and Gram-negative bacteria have been reported to be resistant to quinolones. The resistance appears to be the result of one of three mechanisms: alterations in the quinolone enzymatic targets (DNA gyrase), reduced outer membrane permeability or the development of efflux mechanisms. The accumulation of several bacterial mutations (DNA gyrase and bacterial permeability) has been linked with the development of very high MICs to ciprofloxacin in isolates of *S. aureus, Enterobacteriaceae* species and *P. aeruginosa*. Resistance to quinolones can also develop because of changes in bacterial permeability and the development of efflux pumps. This resistance mechanism is shared with antimicrobial agents structurally unrelated to the quinolones, such as the betalactams, tetracyclines and chloramphenicol (Chloromycetin). Cross-resistance among the quinolones is expected, but the extent to which the MIC is affected varies from agent to agent. Therefore, the bacterial susceptibility and pharmacokinetic profiles of each quinolone should be considered in determining the effectiveness of specific agents.

THERAPEUTIC USES

Urinary Tract Infections

Nalidixic acid is useful only for UTIs caused by susceptible microorganisms. The FQs are significantly more potent and have a much broader spectrum of antimicrobial activity. Norfloxacin is use for UITs and FQs are more effective than trimethoprim-sulfamethoxazole for the treatment of UTIs.

Prostatitis

Norfloxacin, CPFX, and OFLX are effective in the treatment of prostatitis caused by sensitive bacteria. Fluoroquinolones are effective in patients not responding to trimethoprim-sulfamethoxazole [19].

Sexually Transmitted Diseases

The quinolones are contraindicated in pregnancy. Fluoroquinolones (FQs) lack activity for *Treponema pallidum*, *N. gonorrhoeae, C. trachomatis,* and *H. ducreyi.* For chlamydial urethritis/cervicitis, OFLX or sparfloxacin (SPFX) is an alternative treatment with doxycycline or a single dose of azithromycin; other quinolones have not been reliably effective. A single oral dose of FQs such as OFLX or CPFX is effective treatment for sensitive strains of *N. gonorrhoeae,* but increasing resistance to FQs has led to ceftriaxone being the first-line agent for this infection. Pelvic inflammatory disease has been treated with OFLX combined with an antibiotic with activity against anaerobes (clindamycin or metronidazole). Chancroid (infection by *H. ducreyi*) can be treated with CPFX.

Gastrointestinal and Abdominal Infections

For traveler's diarrhea (frequently caused by entero-toxigenic *E. coli*), the quinolones are equal to trimethoprim-sulfamethoxazole in effectiveness [20]. Norfloxacin, CPFX, and OFLX have been effective in the treatment of patients with shigellosis [21]. Norfloxacin is superior to tetracyclines in decreasing the duration of diarrhea in cholera. Ciprofloxacin (CPFX) and OFLX treatment cures most patients with enteric fever caused by *S. typhi,* as well as non typhoidal infections in AIDS patients. Shigellosis is treated effectively with either CPFX or *azithromycin* [22].

Respiratory Tract Infections

The key restriction to the use of quinolones for the treatment of community-acquired pneumonia and bronchitis had been the poor *in vitro* activity of CPFX, OFLX, and norfloxacin against *S. pneumoniae* and anaerobic bacteria. Many newer FQs, including GFLX and moxifloxacin, have excellent activity against *S. pneumoniae.* These newer quinolones shows comparable efficacy to

β-lactam antibiotics [23]. The FQs have activity against the respiratory pathogens, like *H. influenzae, Moraxella catarrhalis, S. aureus, M. pneumoniae, Chlamydia pneumoniae,* and *Legionella pneumophila.* Either a FQ (CPFX or LVFX) or azithromycin is of choice for *L. pneumophila*. The FQs have been very effective against both *H. influenzae* and *M. catarrhalis* from sputum. Mild to moderate activity exhibited against *P. aeruginosa* in patients with cystic fibrosis. The newer FQs are used as single agents for treatment of community-acquired pneumonia [11]. However, have decreasing susceptibility of *S. pneumoniae* to FQs [24].

Bone, Joint, and Soft Tissue Infections

The treatment of chronic osteomyelitis requires prolonged antimicrobial therapy with agents active against *S. aureus* and gram-negative rods. The FQs may be used appropriately in some cases [25]. Bone and joint infections may require treatment with FQs. Dosage should be reduced for patients with severely impaired renal function. Ciprofloxacin (CPFX) should not be given to children or pregnant women. Clinical cures have been as high as 75% in chronic osteomyelitis in which gram-negative rods predominated [11]. Failures have been associated with the development of resistance in *S. aureus, P. aeruginosa,* and *Serratia marcescens.* In diabetic foot infections, which are commonly caused by a mixture of bacteria including gram-negative rods, anaerobes, *streptococci*, and *staphylococci*, the FQs in combination with an agent with anti-anaerobic activity are a reasonable choice. Ciprofloxacin (CPFX) as sole therapy is effective in 50% of diabetic foot infections.

Other Infections

Ciprofloxacin (CPFX) wide usage for the prophylaxis of anthrax and also effective for the treatment of tularemia [26,27]. The FQs may be used as part of multiple-drug regimens for the treatment of MDR-TB and for the treatment of atypical mycobacterial infections as well as *M. avium* complex (MAC) infections in AIDS. In neutropenic cancer patients with fever, the combination of a quinolone with an aminoglycoside (AG) is comparable to β-lactam-AG combinations; quinolones are less effective when used alone. Quinolones, when used as prophylaxis in neutropenic patients, have decreased the incidence of gram-negative rod bacteremias. Ciprofloxacin (CPFX) plus amoxicillin-clavulanate has been effective.

Adverse Effects

Quinolones and FQs generally are well tolerated [28]. The most common adverse reactions involve the GI tract, with 3% to 17% of patients reporting mostly mild nausea, vomiting, and abdominal discomfort. Diarrhea and antibiotic-associated colitis have been unusual. CNS side effects like mild headache and dizziness, in 0.9% to 11% of patients. Rarely, hallucinations, delirium, and seizures have occurred, predominantly in patients who also were receiving *theophylline* or a nonsteroidal anti-inflammatory drug (NSAIDs). Ciprofloxacin (CPFX) and pefloxacin inhibit the metabolism of theophylline, and toxicity from elevated concentrations of the methylxanthine may occur. The NSAIDs may augment displacement of g-aminobutyric acid (GABA) from its receptors by the quinolones [29]. Rashes, including photosensitivity reactions, also can occur. Achilles tendon rupture or tendinitis has occurred rarely. Renal disease, hemodialysis, and steroid use may be predisposing factors [28]. The use of FQs in children has been contraindicated for this reason. However, children with cystic fibrosis given CPFX, norfloxacin, and nalidixic acid have had few, and reversible, joint symptoms [30]. Leukopenia, eosinophilia, and mild elevations in serum transaminases occur rarely. Quinolones probably should be used only with caution in patients treated with amiodarone and quinidine, procainamide as antiarrhythmics (Table 1).

Quinolones and Chemotherapy

Quinolones are classified in four generations. The first generation quinolones are without fluorine as nalidixic acid, cinoxacin and oxolinic acid; the second generation are norfloxacin, CPFX, OFLX, enoxacin and lomefloxacin; the third generation are LVFX, SPFX and GFLX and the fourth generation are MFLX and trovafloxacin (TVFX) [31]. Most recent FQs are being evaluated as potential anti-TB drugs, also for the shorten TB treatment duration, one of the major strategies for TB control [32]. The use of LVFX or MFLX for the treatment of extensively XDR-TB, defined as resistance to INH, RIF, a FQ and a second-line injectable drug, even when OFLX resistance is present [33]. Fluorine-containing nalidixic acid derivatives, the FQs, were introduced into clinical practice in the 1980s [31]. Norfloxacin, the first of a new generation of FQ are antibacterial activity [34]. Substitutions of the FQ molecule resulted in the development of CPFX, a widely used broad spectrum antimicrobial agent [35]. Several modifications of the FQ structure have been attempted in order to develop new expanded antimicrobial agents with improved pharmacokinetic profiles, decreased resistant mutants, reduced adverse effects, and improved efficacy [36,37]. Last-generation FQs share a broad-spectrum antimicrobial activity covering aerobic and anaerobic Gram-positive and Gram-negative bacteria as well as mycobacteria (*M. leprae, M. tuberc*ulosis, M. avium, M. *fortuitum, M. intracellulare, M. kansasii, M. marinum, M. smegmatis* and *M. xenopi*) [38,39]. Fluoroquinolones are widely used for the treatment of infections of the respiratory, gastrointestinal and urinary tracts, sexually transmitted diseases, skin and soft tissue infections and chronic osteomyelitis [40,41]. New FQs are in various phases of clinical development like tosufloxacin, fleroxacin, clinafloxacin, gemifloxacin, rufloxacin, enrofloxacin, difloxacin, amifloxacin, iloxacin, temafloxacin, nadifloxacin, grepafloxacin, balofloxacin, pazufloxacin, prulifloxacin, sitafloxacin, garenoxacin, olamufloxacin [42,43]. In particular MFLX and GFLX are undergoing phase III trials [44,45]. Appreciable efficacies of FQs have also been demonstrated against both *M. fortuitum* infection [46], *M. kansasii,* and *M. xenopi* [47]. Many new FQs indicated for the treatment of respiratory tract infections show excellent activity against MAC isolates [48,49]. The effective antimicrobial activity and clinical efficacy of SPFX, LVFX and GFLX are against MAC infection [50,51]. The FQs also exert clinical efficacy against mycobacteria when they are administered in combination with other drugs including RIF, INH, PZA, ethambutol, and some AGs [52-56]. The value of FQs in the treatment of TB infections may be attributed to the good penetration into infected macrophages where they exert antibacterial activity

[57]. Selected quinolones, on the intracellular activity against *M. tuberculosis* as follows: SPFX and sitafloxacin > LVFX and WQ-3034>olamufloxacin>CPFX and OFLX [58]. Certain drugs, such as rifampin, rifabutin, isiniazid, clofazimine, and some FQs, strongly or moderately reduced the anti-MAC activity [59]. The major problem linked with the use of FQs is the increased incidence of FQ-resistant strains of *M. tuberculosis*, attitude coupled with the absence of cross-resistance or antagonism with other classes of anti-TB agents. Finally, the emergence of MDR-TB strains is related to previous TB treatment of patients with FQs [3].

Table 1: Approved clinical uses for selected fluoroquinolones.

Ciprofloxacin	Acute uncomplicated cystitis in females (oral use only) Urinary tract infections Chronic bacterial prostatitis Uncomplicated cervical and urethral gonorrhea Skin and skin-structure infections Bone and joint infections Infectious diarrhea (oral use only) Typhoid fever (oral use only) Complicated intra-abdominal infections, in combination with metronidazole Acute sinusitis Lower respiratory tract infections Nosocomial pneumonia (iv use only) Empirical therapy for patients with febrile neutropenia, in combination with piperacillin sodium (iv use only) Inhalational anthrax (after exposure) Complicated urinary tract infections and pyelonephritis in pediatric patients (1–17 years old)
Levofloxacin	Uncomplicated urinary tract infections (mild to moderate) Complicated urinary tract infections (mild to moderate) Acute pyelonephritis (mild to moderate) Chronic bacterial prostatitis Uncomplicated skin and skin-structure infections (mild to moderate) Complicated skin and skin-structure infections Acute maxillary sinusitis Acute bacterial exacerbation of chronic bronchitis Community-acquired pneumoniaa Nosocomial pneumonia
Moxifloxacin	Acute bacterial sinusitis Acute bacterial exacerbation of chronic bronchitis Community-acquired pneumoniaa Uncomplicated skin and skin-structure infections Gatifloxacin Uncomplicated urinary tract infections Complicated urinary tract infections Pyelonephritis Uncomplicated urethral and cervical gonorrhea Acute uncomplicated gonococcal rectal infections in women Uncomplicated skin and skin-structure infections
Gemifloxacin	Acute sinusitis Acute bacterial exacerbation of chronic bronchitis Community-acquired pneumonia Acute bacterial exacerbation of chronic bronchitis Community-acquired pneumonia (mild to moderate)[a]

[a]Includes pneumonia due to multidrug-resistant Streptococcus pneumoniae.

Pharmacokinetics

The common adverse effects associated with the use of FQs are gastrointestinal disturbances, nervous system complaints (dizziness, headache), and allergic reactions (skin rashes and pruritus) [60,61]. The use of several FQs have been severely restricted because of advers effects; clinafloxacin causing phototoxicity and hypoglycaemia, SPFX causing phototoxicity [62]. and TVFX causing hepatotoxicity [63]. Grepafloxacin has been withdrawn from the market due to prolongation of the QTc interval. Other FQs such as GFLX, gemifloxacin, LVFX and MFLX have toleraility issues comparable to CPFX. Drug interactions are limited and are infrequent between FQs and other antit-TB drugs [64], however FQ absorption may be reduced when co administered with antacids containing multivalent cations [65,66]. The mechanism by which quinolones enter the bacterial cell is complex [67]. The physicochemical properties of quinolones (hydrophobicity, charge or molecular mass) are important factors for bacterial cell penetration and play a different role in Gram-negative and Gram-positive bacteria. Increasing molecular mass and bulkiness of

substituents at C-7 position hinder penetration of quinolones into Gram-negative bacteria through the porin channels, although hydrophobic molecules appear to enter via the lipopolysaccharide or across the lipid bilayer [68]. Gram-positive bacteria do not possess an outer membrane, therefore lacking outer membrane proteins and lipopolysaccharide. Intracellular accumulation observed in Gram-positive bacteria (e.g. *S. aureus*) is thought to take place by simple diffusion across the cytoplasmic membrane [69]. The unique cell wall structure of mycobacteria is rich in long-chain fatty acids such as C60 to C90 mycolic acids [39]. Mycolic acids are covalently linked to the peptidoglycan-associated polysaccharide arabinogalactan. Moreover, mycobacterial porins, the water-filled channel proteins which form the hydrophilic diffusion pathways, are sparse [70]. A major porin of *M. smegmatis*, MspA, forms a tetrameric complex with a single central pore, but the density of this protein is 50-fold lower than that of porins of gram-negative bacteria [71]. The mycobacterial cell wall functions as an even more efficient protective barrier than the outer membrane of gram-negative bacteria and limits the access of drug molecules to their cellular targets (Table 2).

Structure-activity relationship

The minimal quinolone structure consists of a bicyclic system with a substituent at position N-1, a carboxyl group at position 3, a keto group at position 4, a fluorine atom at position 6 (in case of FQs) (Figure 1) and a substituent (often nitrogen heterocycle moiety) at the C-7. Normally in position 2 there are no substituents, various 1-methyl-2-alkenyl-4(1H)quinolones have been investigated as anti-TB agents [72,73]. The DNA gyrase is most likely the only target of quinolone in M. tuberculosis. The DNA supercoiling inhibition assay may be a useful screening test to identify quinolones with promising activity against M.tuberculosis [74]. They measured the inhibition of DNA supercoiling (IC_{50}) and MIC of several quinolones (Table 3).

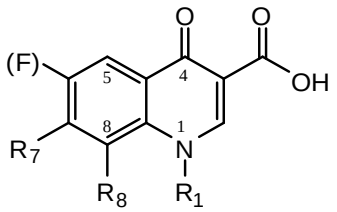
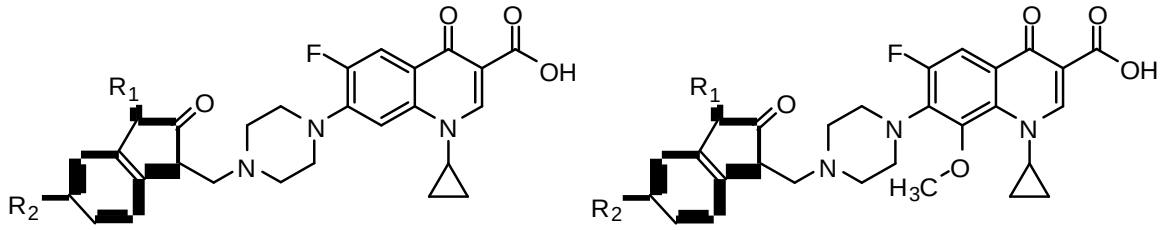


Figure 1: Minimal quinolone structure.

Some quinolones showed high inhibitory activity against M.tuberculosis DNA gyrase, with IC_{50} value below 10 µg/mL. Structure activity relationship (SAR) showed that C-8 with or lacking a substitution, the C-7 ring, the C-6 fluorine, and the N-1 cyclopropyl substituents are advantageous structural features in targeting M. tuberculosis gyrase. The quinolones that showed high potency against M. tuberculosis gyrase are highly active against gram-positive bacteria and definitely were developed for pneumococci (sitafloxacin, SPFX, clinafloxacin, MFLX, and GFLX). Compounds (grepafloxacin, gemifloxacin, TVFX, and the des[6] FQ garenoxacin) with high activity against pneumococci showed only moderate activity against M. tuberculosis gyrase. Most of the FQs developed for their activity against gram negative bacteria (norfloxacin, pefloxacin, enoxacin, fleroxacin, OFLX, temafloxacin, and tosufloxacin) had moderate IC_{50} value except for LVFX and CPFX, which had low IC_{50} value against M. tuberculosis gyrase. In contrast to its effects against pneumococci, the presence of a group at C-5 [75]. or a substituent in the 7-piperazinyl ring [37]. does not seem to improve gyrase affinity. Moreover, the presence of a naphthyridone core (N-8) in gemifloxacin, which has the lowest MIC against gram-positive bacteria, seems adverse effect for a interaction with M. tuberculosis gyrase. Similarly, the naphthyridones tosufloxacin and enoxacin, were only moderately active [76-84]. In general, β-keto carboxylic acid moiety is required for hydrogen bonding interactions with DNA bases in the single stranded regions of double helix of DNA created by the action of the enzyme, and therefore it is essential for the activity [85]. The substituent at N-1 and C-8 positions should be relatively small and lipophilic to enhance self-association. While at C-6 and C-7 positions at fluorine atom and amino group, respectively, appear to be the best. In particular fluorine atom at C-6 improves cell penetration and gyrase affinity [66,85]. The nature of substituent at C-7 position has a great impact on potency, spectrum, solubility and pharmacokinetics. Almost all quinolones have nitrogen heterocycles linked to this position through the heterocyclic nitrogen, extensively investigated are piperazin-1-yl and its 4-substituted derivatives [86]. e.g. various 7-substituted derivatives of CPFX and GFLX (Figure 2), where derivatives bearing R=H and R_1=$NNHCONH_2$ were the most active compounds) have been evaluated for anti-TB activity against M. tuberculosis H37Rv, MDR-TB and XDR-TB strains and for inhibition of the supercoiling activity of DNA gyrase from M. tuberculosis and M. smegmatis. The resulst revealed that usually the increase of lipophilic character of the side chain at C-7 improves the anti-TB activity, without inducing cytotoxicity as demonstrate for balofloxacin ethylene isatin derivatives [87]. Anti-TB activity of cephalosporin conjugates with the piperazinyl ring (Figure 3) at C-7 of the CPFX, both able with antibacterial activity and anti-TB activity [88]. Furthermore, with regard to the substituent at N-1

position, studies confirm that the anti-TB activity is higher for the cyclopropyl and tert-butyl goup than for the 2,4-difluorophenyl and others groups [89,90].

Extensive SAR study showed that an increase in the activity of a given quinolone against gram-positive bacteria does not necessarily lead to increased activity against *M. tuberculosis* [91]. ABT-492 (WQ-3034) is a new FQ that differs from other members of the class by two structural features: a 6-amino-3,5-difluoropyridinyl moiety at position 1 and a 3-hydroxyazetidine-1-yl moiety at position 7 of the 6-FQ core. The antibacterial activity of ABT-492 was significantly greater than that of LVFX. ABT-492 was also more potent than TVFX and CPFX against most quinolone-susceptible pathogens responsible for respiratory tract, urinary tract, bloodstream, and skin infections and against anaerobic pathogens. It was significantly more active than other quinolones against quinolone-resistant gram-positive strains. Furthermore ABT-492 was active against *Chlamydia trachomatis*, indicating good intracellular penetration. Finally, ABT-492 had improved activity against antibiotic-resistant respiratory tract pathogens, including MDR *S. pneumoniae* strains and *Haemophilus influenzae* strains with mutations in DNA gyrase and topoisomerase IV that render them resistant to LVFX [43,92]. However the activity of ABT-492 against *M. tuberculosis* is comparable to or somewhat weaker than that of LVFX and is significantly lower than that of SPFX. The HSR-903 is a newly synthesized quinolone with superior activity against gram-positive cocci [89]. Finally, complexes of the most potent FQs with Pd(II) and Pt(II) ions have been evaluated. Compounds cis-$[MCl_2(L)]$, where L=ciprofloxacin, LVFX, ofloxacin, SPFX, and GFLX, show good anti-TB activity against *M. tuberculosis* H37Rv [93].



Ciprofloxacin derivatives Gatifloxacin Derivatives
R_1 = O, $NNHCONH_2$, $NNHCOCSNH_2$
R_2 = Cl, Br, CH_3

Figure 2: Ciprofloxacin and gatifloxacin 7-substituted derivative.

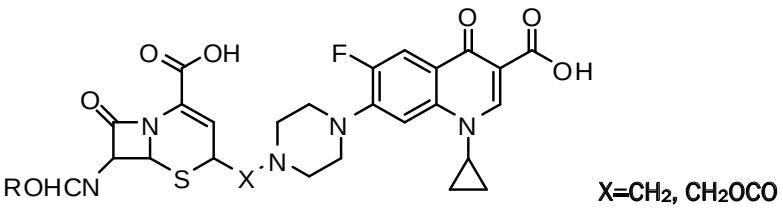


Figure 3: Ciprofloxacin-cephaloosporin conjugates.

Table 3: MIC (µg/mL) of Selected quinolones against Mycobacterium Species (Jacobs. 2004).

QUINOLONES	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
	M. tuberculosis		MACa		M. kansasii		M. fortuitum		M. chelone	
Ciprofloxacin	1	1	-	8-16	1	1-4	1	1	>8	>16
Ofloxacin	1	1-2	16-64	16-128	2	1-4	2	1	>16	>8
Levofloxacin	0.5-4	0.5-16	8-32	1-32	2	0.1-4	2	0.1-4	>8	>8
Sparfloxacin	0.1	0.2-0.5	2-8	4-16	0.5-1	0.2-4	0.5-1	2	>8	>8
Moxifloxacin	-	0.5	-	0.1-2	-	-	-	-	-	-
Gemifloxacin	4	8	-	-	-	-	-	-	-	-
Clinafloxacin	-	1	-	-	-	-	-	-	-	-
Gatifloxacin	0.1-1	0.2-4	2-8	8-16	0.2	2	0.2	1	2	8
Trovafloxacin	32	64	-	-	-	-	-	-	-	-
Sitafloxacin	0.1-1	0.1-2	2-8	8	-	-	-	-	-	-
Grepafloxacin	1	1	-	-	-	-	-	-	-	-

a = M. avium-intracellulare complex

Table 2: Classification on the basis of spectrum of activity.

Class and agent	Half life	Route of administration	Dosage Adjustment required	Significant adverse effects	Significant drug interactions
First generation					
Nalidixic acid (NegGram)	60 to 90 mins	Oral	Renal impairment		Warfarin (Coumadin)
Cinoxacin (Cinobac)	1.1-2.7 hrs	Oral	Renal impairment	Hypersensitivity (fewer than 3 percent of recipients)	
Second generation					
Norfloxacin (Noroxin)	2.3 to 5.5 hours	Oral	Renal impairment		Warfarin, cyclosporine (Sandimmune)
Lomefloxacin (Maxaquin)	7 to 8.5 hours	Oral	Renal impairment	Phototoxicity, headache (3 to 44 percent of recipients), bdominal pain (11 percent), nausea (5.6 percent)	
Enoxacin (Penetrex)	3.3 to 7 hours	Oral Renal or	Hepatic impairment (patients with advanced cirrhosis)	Phototoxicity (mild)	Warfarin, ranitidine (Zantac), bismuth subsalicylate, theophylline, caffeine
Ofloxacin (Floxin)	5 to 8 hours	Oral, intravenous	Renal or hepatic impairment (patients with severe disease)	Insomnia (13 percent of recipients)	Warfarin
Ciprofloxacin (Cipro)	3 to 5.4 hours	Oral, intravenous	Renal impairment	Nausea, vomiting, abdominal pain	Warfarin, theophylline, caffeine, cyclosporine, glyburide (Micronase)
Third generation					
Levofloxacin (Levaquin)	6 hours	Oral, intravenous	Renal impairment	Headache, nausea (6.6 percent of recipients), Diarrhea	
Sparfloxacin (Zagam)	21 hours	Oral	Renal impairment	Phototoxicity (8 percent of recipients), QT interval prolongation, torsades des pointes	Drugs that prolong the QT interval, including classI antiarrhythmics, tricyclic anti-depressants, phenothiazines, cisapride (Propulsid), pentamidine (Pentam) and erythromycin
Gatifloxacin (Tequin)	7 hours	Oral, intravenous	Renal impairment		Same as for sparfloxacin
Moxifloxacin (Avelox)	12 hours	Oral	Hepatic impairment	QT-interval prolongation	Same as for sparfloxacin
Fourth generation					
Trovafloxacin (Trovan) Alatrofloxacin (Trovan IV)	7.8 hours	Oral, intravenous	Hepatic impairment (patients with mild to moderate cirrhosis)	Dizziness (2.4 to 11 percent of recipients), severe hepatotoxicity (rare), candidal vaginitis (1 to 10 percent)	Morphine, citric acid–sodium Intravenous citrate (Bicitra)

CONCLUSION

Quinolines are second-line anti-TB drugs, since their use in TB treatment still remains controversial [94]. On the contrary, they

are suggested and recommended in managing MDR-TB, due to the fact that they have a broad and potent spectrum of activity and can also be administered orally, giving a better chance of cure and preventing the development and spread of further resistance [95]. The 4-quinolones-3-carboxylic acid motif, typical of quinolones, have also recently been reported to display "non-classical" biological activities, such as antitumor, anxiolitic, anti-ischemic, anti-HCV-NS3 helicase and NS5B polymerase activities, anti-HSV-1, anti-HIV-1 integrase and CB-2 agonists [96-98]. However, quinolones remain one of the most widely prescribed antibiotics. In conclusion, we can confirm that in general quinolones are particularly adapted to be used as antitubercular agents.

REFERENCES

1. Sheehan G, Chew NSY. The history of quinolones In Fluoroquinolone Antibiotics. Ronald AR, Low DE (eds) Birkhauser Basel. 2003; 1-10.
2. Ginsburg AS, Grosset JH, Bishai WR. Fluoroquinolones tuberculosis and resistance. Lancet Infect Dis. 2003; 3:432
3. Ginsburg AS, Hooper N, Parrish N, Dooley KE, Dorman SE. Fluoroquinolone resistance in patients with newly diagnosed tuberculosis. Clin Infect Dis. 2003; 37:1448-1452
4. Alland D, Kalkut GE, Moss AR, McAdam RA, Hahn JA, et al. Transmission of tuberculosis in New York City An analysis by DNA fingerprinting and conventional epidemiologic methods. N Engl J Med. 1994; 330:1710-1716
5. Global Tuberculosis Control. Geneva: World Health Organization. 2011.
6. Global tuberculosis control: a short update to the 2010 Report. Geneva: World Health Organization 2010.
7. Getahun H, Gunneberg C, Granich R, Nunn P. HIV infection associated tuberculosis: the epidemiology and the response. Clin Infect Dis, 2010; 50: 201-207.
8. Whalen C, Horsburgh CR, Hom D, Lahart C, Simberkoff M, et al. Accelerated course of human immunodeficiency virus infection after tuberculosis. Am J Respir Crit Care Med. 1995; 51:129-135
9. Eliopoulos GM, Eliopoulos CT. Activity in vitro of the quinolones. In Quinolone Antimicrobial Agents, 2nd (edn). Hooper DC, Wolfson JS (eds), American Society for Microbiology. Washington. 1993; 161-193.
10. Alangaden GJ, Lerner SA. The clinical use of fluoroquinolones for the treatment of mycobacterial diseases. Clin Infect Dis. 1997; 25:1213-1221.
11. Hooper DC. Quinolones. In Mandell Douglas and Bennett's, Principles and Practice of Infectious Diseases. 5th (edn). Mandell GL, Bennett JE, Dolin R (eds), Churchill Livingstone. New York. 2000; 404-423.
12. Medical Letter Gatifloxacin and moxifloxacin: Two new fluoroquinolones. Med Lett Drugs Ther. 2000; 42:15-17
13. Oethinger M, Kern WV, Jellen-Ritter AS, McMurry LM, Levy SB. Ineffectiveness of topoisomerase mutations in mediating clinically significant fluoroquinolone resistance in Escherichia coli in the absence of the AcrAB efflux pump. Antimicrob Agents Chemother. 2000; 44:10-13.
14. Peterson LR, Postelnick M, Pozdol TL, Reisberg B, Noskin GA. Management of fluoroquinolone resistance in Pseudomonas aeruginosa: Outcome of monitored use in a referral hospital. Int J Antimicrob Agents. 1998; 10:207-214.
15. Thornsberry C, Ogilvie P, Kahn J, Mauriz Y. Surveillance of antimicrobial resistance in Streptococcus pneumoniae Haemophilus influenzae and Moraxella catarrhalis in the United States in 1996-1997 respiratory season The Laboratory Investigator Group Diagn Microbiol Infect Dis. 1997; 29:249-257.
16. Drlica K, Zhao X. DNA gyrase topoisomerase IV and the 4-quinolones. Microbiol Mol Biol Rev. 1997; 61:377-392.
17. Alovero FL, Pan XS, Morris JE, Manzo RH, Fisher LM. Engineering the specificity of antibacterial fluoroquinolones: benzenesulfonamide modifications at C-7 of ciprofloxacin change its primary target in Streptococcus pneumoniae from topoisomerase IV to gyrase. Antimicrob Agents Chemother. 2000; 44:320-325.
18. Mitscher LA, Ma Z, Structure-activity relationships of quinolones. In Fluoroquinolone Antibiotics. Ronald AR, Low DE (eds), Birkhauser Basel. 2003; 11-48.
19. Hooper DC, Wolfson JS, Fluoroquinolone antimicrobial agents. New Engl J Med. 1991; 324:384-394.
20. DuPont HL, Ericsson CD, Prevention and treatment of traveler's diarrhea. New Engl J Med. 1993; 328:1821-1827.
21. Bennish ML, Salam MA, Khan WA, Khan AM. Treatment of shigellosis: III Comparison of one- or two-dose ciprofloxacin with standard 5-day therapy A randomized blinded trial. Ann Intern Med. 1992; 117:727-734.
22. Khan WA, Seas C, Dhar U, Salam MA, Bennish ML. Treatment of shigellosis: V Comparison of azithromycin and ciprofloxacin A double-blind randomized controlled trial. Ann Intern Med 1997; 126:697-703.
23. Aubier M, Verster R, Reganney C, Geslin P, Vercken JB, Once-daily sparfloxacin versus high-dosage amoxicillin in the treatment of community-acquired suspected pneumococcal pneumonia in adults Sparfloxacin European Study Group. Clin Infect Dis. 1998; 26:1312-1320.

24. Chen DK, McGeer A, de Azavedo JC, Low DE. Decreased susceptibility of Streptococcus pneumoniae to fluoroquinolones in Canada Canadian Bacterial Surveillance Network. New Engl J Med. 1999; 341:233-239.

25. Gentry LO, Rodriguez-Gomez G. Ofloxacin versus parenteral therapy for chronic osteomyelitis. Antimicrob Agents Chemother. 1991; 35:538-541.

26. Chocarro A, Gonzalez A, Garcia I. Treatment of tularemia with ciprofloxacin. Clin Infect Dis. 2000; 31:623.

27. Swartz MN. Recognition and management of anthrax: An update. New Engl J Med. 2001; 345: 1621-1626.

28. Mandell LA. Improved safety profile of newer fluoroquinolone. In Fluoroquinolone Antibiotics, Ronald AR, Low DE (eds). Birkhauser Basel. 2003; 73-86.

29. Halliwell RF, Davey PG, Lambert JJ. Antagonism of $GABA_A$ receptors by 4-quinolones. J Antimicrob Chemother. 1993; 31:457-462.

30. Burkhardt JE, Walterspeil JN, Schaad UB. Quinolone arthropathy in animals versus children. Clin Infect Dis. 1997; 25:1196-1204.

31. Nora De Souza MV, Rocha Alves Vasconcelos T, Viera de Almeida M, Cardoso SH. Fluoroquinolones: an important class of antibiotics against tuberculosis. Curr Med Chem. 2006; 13: 455-463.

32. Van den Boogaard J, Kibiki GS, Kisanga ER, Boeree MJ, Aarnoutse RE. New drugs against tuberculosis: problems progress and evaluation of agents in clinical development. Antimicrob Agents Chemother. 2009; 53:849-862.

33. Devasia RA, Blackman A, May C, Eden S, Smith T, et al. Sterling TR Fluoroquinolone resistance in Mycobacterium tuberculosis: an assessment of MGIT 960 MODS and nitrate reductase assay and fluoroquinolone cross-resistance. J Antimicrob Chemother. 2009; 63:1173-1178.

34. Appelbaum PC, Hunter PA. The fluoroquinolone antibacterials: past present and future perspectives. Int J Antimicrob. 2000; 16:5-15.

35. Zhanel GG, Ennis K, Vercaigne L, Walkty A, Gin AS, et al. A critical review of the fluoroquinolones: focus on respiratory infections Drugs. 2002; 62:13-59.

36. Stein GE. Pharmacokinetics and pharmacodynamics of newer fluoroquinolones. Clin Infect Dis. 1996; 23:19-24.

37. Domagala JM. Structure-activity and structure-side-effect relationships for the quinolone antibacterials. J Antimicrob Chemother. 1994; 33:685-706.

38. Jacobs MR. Fluoroquinolones as chemotherapeutics against mycobacterial infections. Current Pharm Des. 2004; 10:3213-3220.

39. Brennan PJ, Nikaido H. The envelope of mycobacteria. Annu Rev Biochem. 1995; 64:29-63.

40. Gillespie SH, Morrissey I, Everett DA. Comparison of the bactericidal activity of quinolone antibiotics in a Mycobacterium fortuitum model. J Med Microbiol. 2001; 50:565-570.

41. Huang ES, Stafford RS. National patterns in the treatment of urinary tract infections in women by ambulatory care physicians. Arch Intern Med. 2002; 162:41-47.

42. Jones ME, Critchley A, Karlosky JA, Blosser-Middleton RS, Schmitz FJ, et al. In vitro activities of novel nonfluorinated quinolones PGE 9262932 and PGE 9509924 against clinical isolates of Staphylococcus aureus and Streptococcus pneumonia with defined mutations in DNA gyrase and topoisomerase IV. Antimicrob Agents Chemother. 2002; 46:1651-1657.

43. Tomioka H, Sato K, Kajitani H, Akaki T, Shishido S. Comparative antimicrobial activities of the newly synthesized quinolone WQ-3034 levofloxacin sparfloxacin and ciprofloxacin against Mycobacterium tuberculosis and Mycobacterium avium complex. Antimicrob Agents Chemother. 2000; 44:283-286.

44. Zhang Y. Advances in the treatment of tuberculosis. Clin Pharmacol Ther. 2007; 82:595–600.

45. Von Groll A, Martin A, Jureen P, Hoffner S, Vandamme P, et al. Fluoroquinolone resistance in Mycobacterium tuberculosis and mutations in gyrA and gyrB. Antimicrob Agents Chemother. 2009; 53: 4498-4500.

46. Richeldi L, Covi M, Ferrara G, Franco F, Vailati P, et al. Clinical use of Levofloxacin in the long-term treatment of drug resistant tuberculosis Monaldi. Arch Chest Dis. 2002; 57:39-43.

47. Alvirez-Freites EJ, Carter JL, Cynamon MH. In vitro and in vivo activities of gatifloxacin against Mycobacterium tuberculosis. Antimicrob Agents Chemother. 2002; 46:1022-1025.

48. Rodriguez JC, Cebrian L, Lopez M, Ruiz M, Royo G. Usefulness of various antibiotics against Mycobacterium aviumintracellulare measured by their mutant prevention concentration. Int J Antimicrob Agents. 2005; 25:221-225.

49. Woods GL, Williams-Bouyer BA, Wallace RJ, Brown-Elliott Jr BA, Witebsky FG, et al. Multisite reproducibility of results

obtained by two broth dilution methods for susceptibility testing of Mycobacterium avium complex. J Clin Microbiol. 2003; 41: 627-631.

50. Horiguchi T, Kondo R, Miyazaki J, Shiga M, Sugiyama M, et al Antibacterial activity and clinical efficacy of sparfloxacin in Mycobacterium avium-intracellulare complex infection. J Intern Med Res. 2004; 32:530-539

51. Kobashi Y, Yoshida K, Miyashita N, Niki, Y-Oka M, Relationship between clinical efficacy of treatment of pulmonary Mycobacterium avium complex disease and drug-sensitivity testing of Mycobacterium avium complex isolates. J Infect Chemother. 2006; 12: 195-202.

52. Tomioka H, Sato K, Shimizu T, Sano C. Anti-Mycobacterium tuberculosis activities of new fluoroquinolones in combination with other antituberculous drugs. J Infect. 2002; 44: 160-165.

53. Lu T, Drlica K. In vitro activity of C-8-methoxy fluoroquinolones against mycobacteria when combined with antituberculosis agents. J Antimicrob Chemother. 2003; 52: 1025.

54. Fattorini L, Tan D, Iona E, Mattei M, Giannoni F, et al. Activities of moxifloxacin alone and in combination with other antimicrobial agents against multidrugresistant Mycobacterium tuberculosis infection in BALB/c mice. Antimicrob Agents Chemother. 200; 47: 360-362.

55. Cynamon MH, Sklaney M. Gatifloxacin and ethionamide as the foundation for therapy of tuberculosis. Antimicrob Agents Chemother. 2003; 47: 2442-2444.

56. Tomioka H, Sano C, Sato K, Shimizu T. Antimicrobial activities of clarithromycin gatifloxacin and sitafloxacin in combination with various antimycobacterial drugs against extracellular and intramacrophage Mycobacterium avium complex. Int J Antimicrob Agents. 2002; 19: 139-145.

57. Tomioka H. Prospects for development of new antimycobacterial drugs. J Infect Chemother. 2000; 6: 8-20.

58. Tomioka H. Current status of some antituberculosis drugs and the development of new antituberculous agents with special reference to their in vitro and in vivo antimicrobial activities. Curr Pharm Des. 2006; 12: 4047-4070.

59. Sano K, Tomioka H, Sato K, Sano C, Kawauchi H, et al. Interaction of antimycobacterial drugs with the anti-Mycobacterium avium complex effects of antimicrobial effectors reactive oxygen intermediates reactive nitrogen intermediates and free fatty acids produced by macrophages. Antimicrob Agents Chemother. 2004; 48: 2132-2139.

60. DeAbate CA, McIvor RA, Elvaine P, Gatifloxacin vs. cefuroxime axetil in patients with acute exacerbations of chronic bronchitis. J Respir Dis. 1999; 20: 23-29.

61. Fogarty C, McAdoo MA, Paster R, Gatifloxacin vs. clarithromycin in the management of acute sinusitis J Respir Dis. 1999; 20: 17-22.

62. Lipsky BA, Dorr MB, Magner DJ. 36th Interscience Conference on Antimicrobial Agents and Chemotherapy. 1996; 15-18. New Orleans (CA).

63. Lucena MI, Andrade RJ, Rodrigo L, Salmeron J, Alvarez A, et al. Trovafloxacin induced acute hepatitis. Clin Infect Dis. 2000; 30: 400-401.

64. Berning SE. The role of fluoroquinolones in tuberculosis today. Drugs. 2001; 61: 9-18.

65. Yew WW. Clinically significant interactions with drugs used in the treatment of tuberculosis. Drug Saf. 2002; 25: 111-133.

66. Foroumadi A, Emami S, Mehni M, Moshafi MH, Shafiee A. Synthesis and antibacterial activity of N-[2-(5-bromothiophen-2-yl)-2-oxoethyl] and N-[(2-5-bromothiophen-2-yl)-2-oximinoethyl]derivatives of piperazinyl quinolones. Bioorg Med Chem Letters. 2005; 15: 4536- 4539.

67. Piddock LJ. Mechanism of quinolone uptake into bacterial cells. J Antimicrob Chemother. 1991; 27: 399-403.

68. Dalhoff A, Schmitz FJ. In vitro antibacterial activity and pharmacodynamics of new quinolones. Eur J Clin Microbiol Infect Dis. 2003; 22: 203-221.

69. McCaffrey C, Bertasso A, Pace J, Georgopapadakou NH. Quinolone accumulation in Escherichia coli Pseudomonas aeruginosa and Staphylococcus aureus. Antimicrob Agents Chemother. 1992; 36: 1601-1605.

70. Trias J, Benz R. Permeability of the cell wall of Mycobacterium smegmatis. Mol Microbiol. 1994; 14: 283-290.

71. Engelhardt H, Heinz C, Niederweis M. A tetrameric porin limits the cell wall permeability of Mycobacterium smegmatis. J Biol Chem. 2002; 277: 37567-37572.

72. Wube AA, Hüfner A, Thomaschitz C, Blunder M, Kollroser M, et al. Design synthesis and antimycobacterial activities of 1-methyl-2-alkenyl-4(1H)-quinolones. Bioorg Med Chem. 201; 19: 567-579.

73. Guzman JD, Wube A, Evangelopoulos D, Gupta A Hufner A, et al. Interaction of N-methyl-2-alkenyl-4-quinolones with ATPdependent MurE ligase of Mycobacterium tuberculosis: antibacterial activity molecular docking and inhibition kinetics.

J Antimicrob Chemother. 2011; 66: 1766-1772.

74. Aubry A, Pan XS, Fisher LM, Jarlier V, Cambau E. Mycobacterium tuberculosis DNA gyrase: interaction with quinolones and correlation with antimycobacterial drug activity. Antimicrob Agents Chemother. 2004; 48: 1281-1288.

75. Morris JE, Pan XS, Fisher LM. Grepafloxacin a dimethyl derivative of ciprofloxacin acts preferentially through gyrase in Streptococcus pneumoniae: role of the C-5 group in target specificity. Antimicrob Agents Chemother. 2002; 46: 582-585.

76. Gootz TD, Brighty KE. Fluoroquinolone antibacterials: SAR mechanism of action resistance and clinical aspects. Med Res Rev. 1996; 16: 433-486.

77. Tillotson GS. Quinolones: structure-activity relationships and future predictions. J Med Microbiol. 1996; 44: 320-324.

78. Brighty KE, Gootz TD. The chemistry and biological profile of trovafloxacin. J Antimicrob Chemother. 1997; 39: 1-14.

79. Zhao T, Drlica XK. Gatifloxacin activity against quinoloneresistant gyrase: allele-specific enhancement of bacteriostatic and bactericidal activities by the C-8-methoxy group. Antimicrob Agents Chemother. 1999; 43: 2969-2974.

80. Zhao X, Xu C, Domagala J, Drlika K. DNA topoisomerase targets of the fluoroquinolones: a strategy for avoiding bacterial resistance. Proc Natl Acad Sci. 1997; 94:13991-13996.

81. Zhao BY, Pine BY, Domagala J, Drlika K. Fluoroquinolone action against clinical isolates of Mycobacterium tuberculosis: effects of a C-8 methoxyl group on survival in liquid media and in human macrophages. Antimicrob Agents Chemother. 1999; 43: 661-666.

82. Mizuki Y, Fujiwara I, Yamaguchi T. Pharmacokinetic interactions related to the chemical structures of fluoroquinolones. J Antimicrob Chemother. 1996; 37: 41-55.

83. Bryskier A, Chantot JF. Classification and structure-activity relationships of fluoroquinolones. Drugs. 1995; 49: 16-28.

84. Klopman G, Wang S, Jacobs MR, Ellner JJ. Anti-Mycobacterium avium activity of quinolones: structure-activity relationship studies. J Antimicrob Agents Chemother. 1993; 37: 1807- 1815.

85. Foroumadi A Emami S Hassanzadeh A Rajaee M Sokhanvar K, et al. Synthesis and antibacterial activity of N-(5-benzylthio-134-thiadiazol-2-yl) and N-(5- benzylsulfonyl-134-thiadiazol-2-yl)piperazinyl quinolone derivatives. Bioorg Med Chem Letters. 2005; 15: 4488-4492.

86. Briguglioa I, Pirasa S, Coronaa P, Pirisia MA, Jabesb D, et al. SAR and Anti-Mycobacterial Activity of Quinolones and Triazoloquinolones: An Update. Anti-Infective Agents. 2013; 11: 75-89.

87. Feng LS, Liu ML, Wang B, Chai Y, Hao XQ, et al. Synthesis and in vitro antimycobacterial activity of balofloxacin ethylene isatin derivatives. Eur J Med Chem. 2010; 45: 3407-3412.

88. Zhao G, Miller MJ, Franzblau S, Wanb B, Möllmann U. Syntheses and studies of quinolone-cephalosporins as potential anti-tuberculosis agents. Bioorg Med Chem Letters. 2006; 16: 5534-5537.

89. Sbardella G, Mai A, Artico M, Setzu MG, Poni G, et al. New 6-nitroquinolones: synthesis and antimicrobial activities. Il Farmaco. 2004; 59: 463-471.

90. Shindikar AV, Viswanathan CL. Novel fluoroquinolones: design synthesis and in vivo activity in mice against Mycobacterium tuberculosis H37Rv. Bioorg Med Chem Lett. 2005; 15: 1803-1806.

91. Nilius AM, Shen LL, Hensey-Rudloff D, Almer LS, Beyer JM, et al. In vitro antibacterial potency and spectrum of ABT-492 a new fluoroquinolone. AntimicrobAgents Chemother. 2003; 47: 3260-3269.

92. Tomioka H, Sato K, Akaki T, Kajitani H, Kawahara S, et al. Comparative in vitro antimicrobial activities of the newly synthesized quinolone HSR-903 sitafloxacin (DU-6859a) gatifloxacin (AM-1155) and levofloxacin against Mycobacterium tuberculosis and Mycobacterium avium complex. Antimicrob Agents Chemother. 1999; 43: 3001-3004.

93. Vieira LMM, de Almeida MV, Lourenço MCS, Bezerra FAFM, Fontes APS. Synthesis and antitubercular activity of palladium and platinum complexes with fluoroquinolones. Eur J Med Chem. 2009; 44: 4107–4111.

94. Akashdeep S. Fluoroquinolones should not be the first-line antibiotics to treat community acquired Pneumonia in areas of Tuberculosis endemicity. Clin Infect Dis. 2007; 45: 133.

95. Migliori GB, Lange C, Girardi E, Centis R, Besozzi G, et al. SMIRA/TBNET Study Group Fluoroquinolones: are they essential to treat multidrugresistant tuberculosis?. Eur Respir J. 2008; 31: 904-905.

96. Mugnaini C, Pasquini S, Corelli F. The 4-quinolone-3-carboxylic acid motif as a multivalent scaffold in medicinal chemistry. Curr Med Chem. 2009; 16: 1746-1767.

97. Ahmed A, Daneshtalab M. Nonclassical biological activities of quinolone derivatives. J Pharm Pharmaceut Sci. 2012; 15: 52-72.

98. Asif M, Siddiqui AA, Husain A. Quinolone derivatives as antitubercular drugs. Med Chem Res. 2013; 22: 1029-1042.